new claims 55-58 can be found throughout the specification, including, for example, at pages 35 and 38-40. Thus, this amendment does not add new matter.

The Office objected to page 3 of the specification because the Changeux reference cited at line 13 does not include the year of publication. Applicants have amended the specification to include the date of publication, i.e., May 1991.

The Office requested that applicants amend the title of the application to more closely reflect the claimed subject matter. Applicants have amended the title to recite "TRANSGENIC MICE CONTAINING REGULATORY SEQUENCES OF THE β2-SUBUNIT OF THE NEURONAL NICOTINIC ACETYLCHOLINE RECEPTOR" and thank the Examiner for the suggested title.

The Office notified applicants that the Abstract was not fully legible due to a poor photocopy. Applicants submit herewith a substitute Abstract that has been retyped but is otherwise identical to the originally filed Abstract.

Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner rejected claims 40-47 under 35 U.S.C. § 112, first paragraph, alleging the scope of enablement provided by the specification is not commensurate with the scope of the invention as set forth in the claims. (Paper No. 5, pages 2-7.) Applicants respectfully traverse this rejection.

The Office acknowledges that the specification enables one of skill in the art to make and use a transgenic mouse with a promoter sequence of the β2-subunit of neuronal nicotinic

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acetylcholine receptor that directs expression of a heterologous reporter gene in a tissue-specific manner. (Id. at 3-4.) But the Office asserts that the specification fails to disclose nucleotide sequences encoding other heterologous proteins, including toxins, growth factors, and oncogenic, tumorigenic, or immortalizing proteins, for use in transgene constructs that can expressed at sufficient levels to produce a desired phenotype. (Id. at 4.)

The Office appears to take the position that the specification enables only those transgenic animals disclosed in the working examples. The relevant inquiry for enablement, however, is whether one reasonably skilled in the art could make or use the invention from the disclosures in the specification, coupled with information known in the art, without undue experimentation. (M.P.E.P. § 2164.01.) The test for undue experimentation does not depend on the amount of experimentation, since a considerable amount is permissible as long as it is routine. (M.P.E.P. § 2164.06.) Moreover, the specification preferably omits what is well known. (M.P.E.P. § 2164.08, citing In re Buchner, 929 F.2d 660, 661, 18 U.S.P.Q. 2d 1331, 1332 (Fed. Cir. 1991).)

Applicants disclose the novel promoter sequence of the β2-subunit of neuronal nicotinic acetylcholine receptor gene, and they use this promoter sequence in a transgene construct to direct neuron-specific expression of heterologous reporter genes, such as β-galactosidase and luciferase. Given applicants' teaching, one of skill in the art could replace the reporter gene in the transgene construct with other heterologous sequences without undue experimentation. In fact, Aguzzi et al. (copy enclosed), published in January 1994, discloses well-characterized transgene constructs containing other neuron-specific promoters operatively linked to toxins,

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growth factors, and oncogenic, tumorigenic, or immortalizing proteins. (Aguzzi et al., Abstract, Table 1.) These transgene constructs were used to make transgenic mice and that serve as models of neurological disease. (Id.) In addition, Camper et al. (copy enclosed), published in January 1995, discusses transgene ablation studies in which various toxin genes, including diptheria toxin A, ricin A, and herpes simplex virus thymidine kinase, were linked to different promoters and used to make transgenic animals. (Camper et al. Tables 2-3.) Thus, as of applicants' effective U.S. filing date, December 14, 1994, sequences encoding heterologous proteins, including toxins, growth factors, and oncogenic, tumorigenic, or immortalizing proteins were well known. Moreover, as shown in Aguzzi et al., the skilled artisan knew how to use these heterologous sequences in transgene constructs to direct neuron-specific expression of heterologous proteins. Therefore, as of applicants' filing date, it would not require undue experimentation to incorporate a heterologous sequence, such as one of those disclosed in Aguzzi et al. or Camper et al., into applicants' transgene construct having the promoter sequence of the β2-subunit of neuronal nicotinic acetylcholine receptor gene.

The Office also alleges that the specification fails to disclose any correlation between a specific toxin, growth factor, or oncogenic, tumorigenic, or immortalizing protein and a specific disease state or a particular change of function in the targeted neuron. (Paper No. 5, page 4.) Applicants submit that as of applicants' filing date, this type of information was known within the art, and, therefore, need not be disclosed in the specification. In fact, the specification preferably omits what is well known. (M.P.E.P. § 2164.08, citing In re Buchner, 929 F.2d 660, 661, 18 U.S.P.Q. 2d 1331, 1332 (Fed. Cir. 1991).) For example, Camper et al. describe using

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cell-specific promoters to direct cell-specific expression of immortalizing oncogenes, such as the SV40 T-antigen, in transgenic mice. (Camper et al., page 247, last paragraph.) These mice are useful for developing immortalized cell lines that can be used, for example, to identify cell-specific transcription factors or to examine gene expression. (Id.) Similarly, the skilled artisan would recognize that applicants' claimed transgenic mouse, expressing an oncogenic, tumorigenic, or immortalizing protein, could be used to develop neuronal cell lines, as explained in the specification. (Specification, page 6, lines 12-15.)

In addition, Aguzzi et al. describe the correlation between various heterologous proteins and specific disease states, including the SV40 T antigen and leukodystrophy (pages 11-12), JC viral antigens and leukoencephalopathy (page 12), neurofilament light and heavy chains and amyotrophic lateral sclerosis and infantile spastic muscular atrophy (page 12), proteins encoded by *c-mos* and *v-mos* oncogenes and neurodegeneration (page 13), and CuZn-superoxidase dismutase and neurodegeneration (pages 13-14). Thus, as of applicants' filing date, correlations were known to exist between heterologous proteins and specific diseases.

The Office further asserts that the specification fails to disclose an expression level of the toxin that produces the desired phenotype without being lethal to the mouse. (Paper No. 5, page 4.) In response, applicants submit that determining an appropriate nonlethal expression level is a matter of routine screening and does not amount to undue experimentation. One of skill in the art would be prepared to screen negative transgenic mice to find one with the desired phenotype. Cf. In re Wands, 858 F.2d 731, 740, 8 U.S.P.Q.2d 1400, 1406 (Fed. Cir. 1988) (finding that practitioners are prepared to screen negative hybridomas in order to find one that makes the

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desired antibody). Moreover, since transgenic mice with lethal expression levels do not survive, they will be readily distinguishable from transgenic mice with nonlethal expression levels.

The Office also asserts that as of the filing date of the application, the art of transgenic animals was unpredictable. More specifically, citing a ***1991*** Palmiter et al. reference, the Office asserts that the two most common problems with cell-specific gene expression are "inappropriate expression patterns and failure to achieve adequate expression levels." (Paper No. 5, page 5.) The Office also cites a ***1992*** reference, Kappel et al., for its teaching that "inherent cellular mechanisms may alter the pattern of gene expression." (Id.) Finally, the Office relies on a passage under the heading "Transgene Regulation and Expression" at page 256 of Cameron (1997) to further support its position that transgene expression is unpredictable. Although the Cameron reference was published in 1997, all the references cited in this passage about transgene regulation and expression (i.e., references 52-60) were published in or before ***1988***—more than six years before applicants' filing date. Thus, none of the references cited by the Office, Palmiter et al., Kappel et al., or Cameron, accurately represents the state of the transgenic art as of applicants' December 14, 1994, filing date.

On the other hand, applicants submit that Aguzzi et al. and Camper et al. dated January 1994 and January 1995, respectively, more closely reflect the state of the art as of the filing date of the instant application. Aguzzi et al. and Camper et al. demonstrate that by late 1994, it was well within the skill of the art to direct tissue-specific expression of genes in transgenic mice using tissue-specific promoters. In addition, as discussed above, these references show that as of 1994, those skilled in the art were using these transgenic mice to direct tissue-specific expression

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of genes encoding toxins, growth factors, and oncogenic, tumorigenic, or immortalizing proteins and that such transgenic mice could be used, for example, to develop disease models, to develop cell lines, or to gain a better understanding of tissue-specific gene expression. Furthermore, Aguzzi et al. demonstrate *neuron*-specific expression of genes in transgenic mice, using neuron-specific promoters. Applicants disclose a novel, neuron-specific promoter and the use of this promoter in transgenic mice to direct neuron-specific expression of a heterologous protein. Thus, given applicants' disclosure coupled with what was known in the art, the skilled artisan could combine applicants' novel promoter sequence with known heterologous sequences to generate transgenic mice without undue experimentation.

As further evidence that the specification enables one of skill in the art to make and use applicants' claimed transgenic, applicants submit a copy of U.S. Patent 4,873,316 to Meade et al. The Meade et al. patent issued on October 10, 1989, from an application filed on June 23, 1987. Meade et al. generated a transgenic mouse having a milk-specific promoter (casein promoter) coupled to a sequence encoding a heterologous ("exogenous") tissue plasminogen activator (TPA) protein. Meade et al. disclosed only one working example in which TPA expression was directed to the mammary glands of a transgenic mouse. The Patent Office, however, allowed claims directed broadly to processes of producing "exogenous" protein using transgenic mammals having a casein promoter linked to an "exogenous" sequence. (Meade et al., claim 1.) The claims were not limited to the single embodiment disclosed in the working example in which the exogenous sequence encoded TPA. Rather, the claims encompass transgenic mice having the casein promoter linked to any "exogenous" sequence. According to 35 U.S.C. § 282,

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every patent is presumed valid and is thus presumptively enabled. (M.P.E.P. §§ 716.07 and 1701.) Therefore, applicants do not understand how the Office can hold the instant application to a higher enablement standard than Meade et al., which was filed more than seven years before this application. If anything, the standard should be lower given the higher level of skill in the art resulting from advancements in the transgenic art during the intervening seven years between the filing date of Meade et al. and this application.

Claims 41-45 are directed to transgenic mice generated by crossing a first transgenic mouse with a second mouse. The Office asserts that these claims are not enabled alleging that the specification does not disclose a phenotype associated with the transgenic mouse or the resulting phenotype displayed by the progeny obtained by crossing the first transgenic mouse with a second mouse. (Paper No. 5, page 6.) As explained above, the phenotype of the transgenic mice depends on the expressed heterologous protein. Therefore, one of skill in the art would know the desired phenotype based on the selected heterologous protein. As for the resulting phenotype of the progeny obtained by crossing the first transgenic mouse with a second mouse, the progeny would similarly express the heterologous protein and thus retain the desired phenotype of the first transgenic mouse.

The Office rejected claims 46 and 47, directed to processes for producing a neuronal host cell that expresses a heterologous protein, alleging that the specification does not disclose how to transfer DNA sequences to neuronal cells *in vivo*, 2) the amount of DNA sequence needed to obtain transgene expression upon transfer into host neuronal cells, and 3) the physiological effect

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of DNA transfer on the neuronal host cell. (Paper No. 5, page 7.) Applicants respectfully disagree.

The processes of claims 46 and 47 involve transferring to a neuronal host cell a DNA sequence comprising a promoter of the β2-subunit of neuronal nicotinic acetylcholine receptor linked to a nucleotide sequence encoding a heterologous polypeptide "under suitable conditions to cause expression of the heterologous polypeptide by the neuronal host cell." Page 35 of the specification describes generating transgenic mice having the β2-promoter sequence coupled to the *nlsLacZ* gene. Similarly, page 38 describes generating transgenic mice having the β2-promoter sequence coupled to the *nls*- β-galactosidase gene. As shown in the specification, these transgenic mice express the *lacZ* and β-galactosidase genes *in vivo*, permitting the detection and isolation of neuronal cell populations in which the transgene is expressed. (Specification, page 35, lines 7-16, pages 39-40; page 6, lines 15-18.) Thus, the specification teaches the transfer of DNA sequences *in vivo* to neuronal cells.

Since the specification does not disclose any working examples involving a transgene with a DNA sequence encoding a heterologous toxin, or oncogenic, tumorigenic or immortalizing protein, the Examiner further asserts that one of skill in the art would not know how to use a neuronal host cell that expresses such a heterologous protein. (Paper No. 5, page 7.) Applicants respectfully disagree. As discussed previously, Aguzzi et al. and Camper et al. demonstrate that as of applicants' filing date, one of skill in the art would know how to use neuronal host cells expressing heterologous toxins or oncogenic, tumorigenic or immortalizing proteins. Aguzzi et al, in particular, provide numerous examples of transgenic mice exhibiting

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neuron-specific expression of heterologous toxins. (Aguzzi et al., Table 1.) In addition, as explained in the specification, transgenic mice exhibiting neuron-specific expression of an oncogenic, tumorigenic, or immortalizing protein are useful for developing neuronal cell lines. (Specification, page 6, lines 12-15.)

For the reasons discussed above, the specification provides an enabling disclosure that is commensurate in scope with the claimed subject matter. Accordingly, applicants respectfully request withdrawal of this 35 U.S.C. § 112, first paragraph, rejection.

Rejections Under 35 U.S.C. § 112, Second Paragraph

In Paper No. 5, the Examiner rejected claims 41-45 under 35 U.S.C. § 112, second paragraph, as indefinite for allegedly failing to particularly point out and distinctly claim the subject matter that applicants regard as their invention. (Paper No. 5, page 7.)

Specifically, the Examiner alleged that the phrase "and wherein the neurons of the transgenic mouse express the heterologous polypeptide" renders claim 41 indefinite because it is unclear whether the phrase refers to the "first mouse" or the "transgenic mouse" generated by crossing the first and second mouse. Applicants respectfully traverse this rejection.

Claim 41 identifies three mice: a first mouse, a second mouse, and a transgenic mouse generated by crossing the first and second mouse. When describing the first mouse in claim 41, applicants use proper antecedent basis and refer specifically to "the first mouse." Similarly, applicants use proper antecedent basis when referring to "the transgenic mouse." Therefore, in the phrase "wherein the neurons of the transgenic mouse express the heterologous polypeptide," the term "the transgenic mouse" refers back to "[a] transgenic mouse generated by crossing a

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first mouse with a second mouse," which is recited in the first line of the claim. If applicants had been referring to the first mouse in this phrase, they would have used the term "the first mouse" instead of "the transgenic mouse." Accordingly, applicants respectfully assert that claim 41 is neither vague nor indefinite and respectfully request withdrawal of this rejection.

The Office also asserted that claim 43 is rendered vague and indefinite by the phrase "the DNA of the second mouse is not identical to the DNA of the first mouse." (Paper No. 5, page 7.) According to the Office, it is unclear whether the term DNA refers to endogenous DNA or some other type of DNA and, therefore, it is unclear whether the second mouse is a different strain than the first mouse or is not a transgenic sibling of the second mouse. (Id.) Applicants respectfully traverse this rejection.

According to the plain meaning of the phrase in question, the DNA of the second mouse has some difference in nucleotide sequence compared to the DNA of the first mouse. Thus, the second mouse could belong to a different strain than the first mouse, since there would be some genetic difference between the two strains. Similarly, the second mouse could be a transgenic sibling of the first mouse provided they are not genetically identical. Therefore, applicants respectfully request withdrawal of this rejection.

The Office rejected claim 44 asserting that the phrase "the second mouse is a transgenic mouse containing a different transgene than the first mouse" is vague and indefinite. (Paper No. 5, page 8.) The Office asserted that it was unclear from the specification and the claim which transgenes are encompassed by the claim. (Id.)

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Although applicants respectfully disagree with this rejection, in an effort to expedite prosecution, applicants have amended claim 44. As amended, claim 44 recites that the "the second mouse is a transgenic mouse containing *a DNA sequence* different from *the DNA sequence* of the first mouse." Claim 44 depends indirectly from claim 41. Since claim 41 describes a first mouse containing a "DNA sequence comprising ..." the term "the DNA sequence" in claim 44 has direct antecedent basis. Therefore, applicants respectfully assert that there is nothing vague or indefinite about a second mouse containing "a DNA sequence different from the DNA sequence of the first mouse." Thus, applicants respectfully request withdrawal of this rejection. This amendment does not narrow the scope of claim 44.

Double Patenting Rejection

The Examiner provisionally rejected claim 40 under the judicially created doctrine of obviousness type double patenting over claim 15 of copending Application No. 08/465,712 ("the '712 application"). (Paper No. 5, page 8.) Although the claims of the '712 application have been allowed, applicants are currently awaiting a decision from the PTO regarding a Petition to Withdraw Holding of Abandonment, which was filed in the '712 application. Therefore, until the '712 application issues as a patent, applicants respectfully request that the Examiner hold this provisional rejection in abeyance.

CONCLUSION

In view of the foregoing amendments and remarks, applicants respectfully request reconsideration and reexamination of this application and timely allowance of the pending claims.

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Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account no. 06-0916.

Respectfully submitted,

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